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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/668,778

09/22/2003

Robert F. Balint

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EXAMINER

EPPERSON, JON D

ART UNIT

PAPER NUMBER

1639

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
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3 MONTHS

01/05/2007

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/668,778	<b>Applicant(s)</b> BALINT ET AL.	
	<b>Examiner</b> Jon D. Epperson	<b>Art Unit</b> 1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 25 October 2006.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 63, 64 and 66-74 is/are pending in the application.
- 4a) Of the above claim(s) 64 and 68-70 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 63, 66, 67 and 71-74 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                                | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

## DETAILED ACTION

### *Request for Continued Examination (RCE)*

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/25/06 has been entered. Claims 63-74 were pending. Applicants canceled claim 65 and amended claims 63 and 66. Therefore, claims 63, 64 and 66-74 are currently pending. Claims 64 and 68-70 are drawn to non-elected species and/or inventions and thus these claims remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b), there being no allowable generic claim. Therefore, claims 63, 66, 67 and 71-74.

Those sections of Title 35, US code, not included in the instant action can be found in previous office actions.

### *Priority*

2. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 1290 and/or 119(e) as follows:

This application is a CON of 09/526,106 03/15/2000 ('106), which claims benefit of 60/175,968 filed 01/13/2000 ('968) and claims benefit of 60/135,926 filed on 05/25/1999 ('926)

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and claims benefit of 60/124,339 filed on 03/15/1999 ('339). However, one or more of the applications stated above fail to provide adequate support under 35 U.S.C. § 112, first paragraph for the claimed invention as follows:

(A) For *claims 63, 66, 67 and 71-74*, none of the applications provide support for the current genus of fragment complementation systems wherein "wherein said first Class A  $\beta$ -lactamase protein break-point and said second Class A  $\beta$ -lactamase protein break-point are within 10 amino acids in either direction from a junction between 2 amino acid residues, wherein said 2 amino acid residues are within a solvent exposed loop between elements of secondary structure" (e.g., see New Matter Rejection below). In addition, Applicants are not in possession of fragments less than 25 amino acids long (e.g., see New Matter Rejection below). In addition, there is no support for the P149/N150, E172/L173, K190/V191, G203/K229 junctions in claim 67 (e.g., see New Matter rejection below).

(B) For claims 68-70 and 72-74, the '339 application fails to provide support for peptides segments that "enhance" functional reconstitution including HSE, EKR, QGN, DGR, GRR, and GNS.

(C) For claims 68-70 and 72-74, the '926 application fails to provide support for peptides segments that "enhance" functional reconstitution including HSE, EKR, QGN, DGR, GRR, and GNS.

If applicant believes this assessment is in error, applicant must disclose where in the specification support for these limitations can be found. See MPEP § 714.02. Therefore the filing date of the instant application is deemed to be its actual filing date, **September 22, 2003**.

3. Applicant states that this application is a continuation or divisional application of the prior-filed application (see above). A continuation or divisional application cannot include new matter. Applicant is required to change the relationship (continuation or divisional application) to continuation-in-part because this application contains the following matter not disclosed in the prior-filed application: See New Matter rejection below.

#### **Withdrawn Objections/Rejections**

4. The Michnick et al. rejections under 35 U.S.C. § 103(a) are withdrawn in view of

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Applicants' arguments and/or amendments. The provisional double patenting rejection is over application 09/526,106 is withdrawn in view of Applicants' express abandonment of that application. The provisional double patenting rejection over application 10/330,811 is withdrawn in view of Applicants' cancellation of claims 1, 12 and 13.

### **New Rejections**

#### ***Claim Rejections - 35 USC § 112, second paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 63, 66, 67 and 71-74 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. **Claim 63** recites the limitations "wherein said first Class A  $\beta$ -lactamase protein break-point and said second Class A  $\beta$ -lactamase protein break-point ..." in the newly added amendment. There is insufficient antecedent basis for this limitation in the claim. The claim previously refers to a first and second "oligopeptide," not a first and second "break-point." Correction is requested.

#### ***Claims Rejections - 35 U.S.C. § 112, first paragraph***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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6. Claims 63, 66, 67 and 71-74 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed had possession of the claimed invention. This is a new matter rejection.

A. Claim 63 was amended in the 10/25/06 response. However, the Examiner cannot find support for these amendments. Specifically, the specification does not provide support for “wherein said first Class A  $\beta$ -lactamase protein break-point and said second Class A  $\beta$ -lactamase protein break-point are within 10 amino acids in either direction from a junction between 2 amino acid residues, wherein said 2 amino acid residues are within a solvent exposed loop between elements of secondary structure and.” Although this claim limitation was submitted in a preliminary amendment on the filing date, such an amendment is not considered part of the original disclosure unless the application was filed on or after September 21, 2004. See 37 CFR 1.115. In addition, prior practice did not consider such an amendment as part of the original disclosure either unless it was referred to in the first executed oath. This has not been done.

Although Applicants previously stated that support can be found at page 13, lines 16-19 and page 16, lines 25-28 (e.g., see 9/22/03 arguments, pages 2 and 3), upon further consideration the Examiner cannot agree. The specification at page 16, lines 27-28 reads, “the actual break-point could be within ten amino acid residues in either direction from an identified functional contiguous break-point junction.” However, this statement does not refer to page 13, lines 16-19 as implied but, rather, the lines immediately above it

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(i.e., on the same page), which indicates that the only "identified functional contiguous break-point junction" is E197/L198 or perhaps the broad 195-202 positions (e.g., see page 16, lines 10-15, "An exposed loop was identified by this method between two  $\alpha$ -helixed of E. coli TEM-1  $\beta$ -lactamase (approximately Thr195 to Ala202, between helixes 7 and 8) within which the chain could be broken to produce fragment which could only complement for activity when fused to fos and jun helixes. Representative fragments with contiguous break point termini at Glu197 and Leu198 were designated  $\alpha$ 197 (N-terminal fragment) and  $\omega$ 198 (C-terminal fragment), and subsequently shown to produce selectable activity." Thus, it would appear that only one loop (i.e., Thr195 to Ala202) was identified, not all loops as currently claimed. In addition, the specification at page 16, lines 4 and 5 reads, "Fragments of less than 25 amino acids were considered non-viable." Therefore, Applicants' are not in possession of fragments < 25 amino acids.

In addition, the Examiner cannot find support for the junctions set forth in claim 67 including P149/N150, E172/L173, K190/V191, G203/K229. This was not addressed in the 9/22/03 arguments. If Applicants believe this to be in error, Applicants should set forth page and line number to show support.

### ***Claims Rejections - 35 U.S.C. § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 63, 66, 67, 71 and 72 are rejected under 35 U.S.C. 102(b) as being anticipated by Wehrman et al. (Wehrman et al. "Protein-protein interactions monitored in mammalian cells via complementation of  $\beta$ -lactamase enzyme fragments" *PNAS* **March 19, 2002**, 99(6), 3469-3474) (3/18/04 IDS, AB).

For *claim 63*, Wehrman et al. (see entire document) disclose a  $\beta$ -lactamase complementation system (see Wehrman et al., abstract), which anticipates the claimed invention. For example, Wehrman et al. disclose a fragment complementation system (e.g., see abstract and title) said system comprising a first oligopeptide comprising an N-terminal fragment of a Class A  $\beta$ -lactamase protein covalently bonded through the C-terminus of a first Class A  $\beta$ -lactamase protein break-point to a first interactor domain (e.g., see figure 1A; see also page 3470, column 2, second to last paragraph wherein the "197  $\beta$ -lactamase fragment was fused to the amino terminus of the Fos helix [i.e., an interactor domain]"). Wehrman et al. also disclose a second oligopeptide comprising a C-terminal fragment of a Class A  $\beta$ -lactamase protein covalently bonded through the N-terminus of a second Class A  $\beta$ -lactamase protein breakpoint to a second interactor domain (e.g., see figure 1A; see also page 3470, column 2, second to last paragraph wherein the "198 fragment fused to the carboxyl terminus of the Jun helix [i.e., an interactor domain]"). In addition, Wehrman et al. disclose said first Class A  $\beta$ -lactamase protein break-point and said second Class A  $\beta$ -lactamase protein break-point are within 10 amino acids in either direction from a function between 2 amino acid residues wherein said 2 amino acid residues are within a solvent exposed loop between elements of



secondary structure (e.g., see figure 1 wherein 197/198 junction is disclosed). Finally, Wehrman et al. disclose binding of said first interactor domain with said second interactor domain said N-terminal fragment and said C-terminal fragment functionally reconstitute to form the Class A B-lactamase protein (e.g., see abstract; see also Results section; see also figures 2-4).

For *claim 66*, Wehrman et al. disclose fragment complementation wherein said Class A  $\beta$ -lactamase protein comprises SEQ ID NO 2 (e.g., see figure 1).

For *claim 67*, Wehrman et al. disclose a fragment complementation system wherein said first B-lactamase protein break-point and said second B-lactamase protein break-point are within 10 amino acids in either direction from a junction between 2 amino acid residues in SEQ ID NO 2 selected from the group consisting of P149 and N150 E172 and L173 K190 and V191 A202 and G203 and G228 and K229 (e.g., see figure 1 wherein the 197/198 break occurs within 10 amino acids of K190/V191 and A202/G203).

For *claim 71*, Wehrman et al. disclose a fragment complementation system of wherein said first oligopeptide further comprises a first polypeptide linker that separates the N-terminal fragment of a Class A B-lactamase protein from the first interactor domain wherein said first polypeptide linker is 3-30 amino acids in length and said second oligopeptide further comprises a second polypeptide linker that separates the C-terminal fragment of a Class A B-lactamase protein from the second interactor domain wherein said second polypeptide linker is 3-30 amino acids in length (e.g., see figure 1;

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see also page 3470, column 2, second to last paragraph wherein the (Gly4Ser)<sub>3</sub> linker is disclosed for each).

For *claim 72*, Wehrman et al. disclose, for example, HSE GRE EKR and NGR (e.g., see page 3471, column 1, paragraph 1; see also page 3470, column 2, last two paragraphs).

***Claims Rejections - 35 U.S.C. § 102/103***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in

(1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or

(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 63, 66, 67, and 71 are rejected under 35 U.S.C. § 102(e) as anticipated by or, in the alternative, 35 U.S.C. § 103(a) as being unpatentable over Michnick et al. (U.S. Patent No. 6,828,099) (Filed May 31, 2001) alone or in view of Galarneau et al. (Galarneau et al., “ $\beta$ -Lactamase protein fragment complementation assays as *in vivo* and *in vitro* sensors of protein-protein interactions” *Nature Biotechnology* **2002**, *20*, 619-622) as further evidenced if necessary by Applicants’ Exhibit 1 filed 10/25/06.

For **claim 63**, Michnick et al. (see entire document) disclose protein fragment complementation systems for the detection of protein-protein and protein-small molecule interactions (e.g., see Michnick et al., abstract), which anticipates the claimed invention. For example, Michnick et al. disclose a fragment complementation system (e.g., see abstract) said system comprising a first oligopeptide comprising an N-terminal fragment of a Class A  $\beta$ -lactamase protein covalently bonded to a first Class A B-lactamase protein break-point to a first interactor domain (e.g., see Example 2 wherein FRB-5a.a.-BLF[1] is disclosed, in this scenario FRB = interactor domain and BLF[1] = 23-197 of TEM-1  $\beta$ -lactamase fragment). In addition, Michnick et al. disclose a second oligopeptide comprising a C-terminal fragment of a Class A  $\beta$ -lactamase protein covalently bonded to a second Class A B-lactamase protein breakpoint to a second interactor domain (e.g., see Example 2 wherein FKBP-5a.a.-BLF[2] is disclosed, in this scenario FKBP is the

interactor domain and BLF[2] = 198-286 of TEM-1  $\beta$ -lactamase fragment). Michnick et al. do not explicitly disclose a  $\beta$ -lactamase protein covalently bonded “through the C-terminus” of a first class A  $\beta$ -lactamase protein break-point to a first interactor domain and a second oligopeptide comprising a C-terminal fragment of a Class A  $\beta$ -lactamase protein covalently bonded “through the N-terminus” of a second class A  $\beta$ -lactamase protein break-point to a second interactor domain (i.e., this corresponds to the “insert” orientation disclosed in figure 2 of Galarneau et al. wherein a 15 amino acid linker was used to connect to two fragments with the claimed orientation instead of two interactor domains). To the contrary, Michnick et al. disclose just the opposite orientation (i.e., the “circular permutation” orientation, see Galarneau et al., figure 2) wherein a  $\beta$ -lactamase protein is covalently bonded “through the N-terminus” away from the first class A  $\beta$ -lactamase protein break-point to a first interactor domain and a second oligopeptide comprising a C-terminal fragment of a Class A  $\beta$ -lactamase protein is covalently bonded “through the C-terminus” of a second class A  $\beta$ -lactamase protein away from break-point to a second interactor domain. However, the Examiner contends that both orientations would be immediately envisioned because these are the “only two” orientations that preserve protein folding as exemplified, for example, by Applicants’ exhibit 1 (submitted 10/25/06). That is, protein folding is only preserved when a linker or pair of interactor domains bind to the same side of the protein (i.e. see exhibit 1, top figure), not to opposite ends (i.e., see exhibit 1, bottom figure). Therefore, a person of skill in the art would immediately envision both the “insert” and “circular permutation” orientations. *In re Petering* 133 USPQ 275 (CCPA 1962); see also *In re Schauman*, 572 F.2d 312, 197

USPQ 5 (CCPA 1978); see also MPEP § 2131. Alternatively, Michnick et al. inherently disclose this feature in accordance with *In re Graves*, 69 F.3d 1147, 36 USPQ2d 1697 (Fed. Cir. 1995) (prior art reference disclosing a system for testing the integrity of electrical interconnections that did not specifically disclose simultaneous monitoring of output points still anticipated claimed invention if simultaneous monitoring is within the knowledge of a skilled artisan). Here, fusions in the claimed orientation are shown to be within the knowledge of a skilled artisan by Galarneau et al. (e.g., see Galarneau et al., figure 2) showing the proper orientation in the QI construct using linker instead of a pair of interactor domains.

In addition, Michnick et al. disclose said first Class A  $\beta$ -lactamase protein break-point and said second Class A B-lactamase protein break-point are within 10 amino acids in either direction from a function between 2 amino acid residues wherein said 2 amino acid residues are within a solvent exposed loop (e.g., see Example 2 wherein the break-point is at positions 197/198, see also column 2, lines 17-33 indicating that positions 196-200 form a solvent exposed loop; see also figure 1). Finally, Michnick et al. disclose binding of said first interactor domain with said second interactor domain said N-terminal fragment and said C-terminal fragment functionally reconstitute to form the Class A  $\beta$ -lactamase protein (e.g., see figure 4; see also column 3, first full paragraph; see also column 5, lines 43-54).

For **claim 66**, Michnick et al. also disclose a Class A  $\beta$ -lactamase protein comprises SEQ ID NO 2 (e.g., see Example 2; see also column 1, line 33 disclosing accession number AAB59737).

For *claim 67*, Michnick et al. also disclose said first  $\beta$ -lactamase protein break-point and said second  $\beta$ -lactamase protein break-point are within 10 amino acids in either direction from a junction between 2 amino acid residues in SEQ ID NO 2 selected from the group consisting of P149 and N150 E172 and L173 K190 and V191 A202 and G203 and G228 and K229 (e.g., see Example 2 wherein the 197/198 break-point is disclosed that is within 10 amino acids of K190/V191 or A202/G203).

For *claim 71*, Michnick et al. also disclose a fragment complementation wherein said first oligopeptide further comprises a first polypeptide linker that separates the N-terminal fragment of a Class A  $\beta$ -lactamase protein from the first interactor domain wherein said first polypeptide linker is 3-30 amino acids in length and said second oligopeptide further comprises a second polypeptide linker that separates the C-terminal fragment of a Class A  $\beta$ -lactamase protein from the second interactor domain wherein said second polypeptide linker is 3-30 amino acids in length (e.g., see Example 2 disclosing the 5 amino acid linker Gly-Gly-Gly-Gly-Ser in each case).

In the alternative that the prior art teachings of Michnick et al. differ from the claimed invention, the difference is set forth as follows:

For *claim 63*, Michnick et al. fail to teach the a  $\beta$ -lactamase protein covalently bonded “through the C-terminus” of a first class A  $\beta$ -lactamase protein break-point to a first interactor domain and a second oligopeptide comprising a C-terminal fragment of a Class A  $\beta$ -lactamase protein covalently bonded “through the N-terminus” of a second class A  $\beta$ -lactamase protein break-point to a second interactor domain (i.e., this corresponds to the “insert” orientation disclosed in figure 2 of Galarneau et al. wherein a

15 amino acid linker was used to connect to two fragments with the claimed orientation instead of two interactor domains). To the contrary, Michnick et al. disclose just the opposite orientation (i.e., the “circular permutation” orientation, see Galarneau et al., figure 2) wherein a  $\beta$ -lactamase protein is covalently bonded “through the N-terminus” away from the first class A  $\beta$ -lactamase protein break-point to a first interactor domain and a second oligopeptide comprising a C-terminal fragment of a Class A  $\beta$ -lactamase protein is covalently bonded “through the C-terminus” of a second class A  $\beta$ -lactamase protein away from break-point to a second interactor domain.

However, Galarneau et al. teach the following limitations that are deficient in Michnick et al.:

For *claim 63*, Galarneau et al. (see entire document) teach the use of rejoining the fragments (albeit with a linker instead of a pair of interactor domains) using the currently claimed orientation (e.g., see figure 2 wherein the QI construct possesses a linker that joins the BLF[1] fragment to the BLF[2] fragment at the 196/198 junction).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to join the interactor domains to the BLF[1] and BLF[2] fragments using their C- and N-termini, respectively (referred to as the “insert” orientation), because Galarneau et al. show that this orientation will not destroy the proper folding and hence activity of the enzyme (e.g., see figure 2, QI construct).

Furthermore, a person of ordinary skill in the art would have been motivated to use this orientation instead of the reverse N- and C- termini for BLF[1] and BLF[2], respectively (referred to as the “circular permutation” orientation), because Galarneau et al. disclose

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that the "insert" orientation retains approximately 40% of the enzymes wild type activity whereas the "circular permutation" orientation retains only about 20% of the enzymes wild type activity (i.e., the "insert" activity is twice as good). Finally, a person of skill in the art would reasonably have expected to be successful because the "insert" orientation does not destroy the proper folding of the enzyme by "reversing" on of the subunits.

### *Conclusion*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.  
December 23, 2006

**JON EPPERSON  
PRIMARY EXAMINER**

